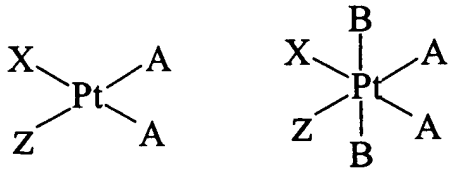
II. REMARKS

Summary of the Invention

This section is included for the convenience of the Examiner to describe the invention as claimed herein.

The claims, as amended herein, relate to the area of platinum antitumor drugs which are active against cancer cells and have improved aqueous solubility and activity. In general, the greater aqueous solubility of the claimed complexes allow for an easier formulation and administration of the drug. This is particularly important for intravenous administration - a higher aqueous solubility would allow for a higher drug dose to be intravenously administered in a smaller volume of saline.

In particular, the invention provides a ***cis*-platinum complex** of the formula Ia or Ib



Ia Ib

or a pharmaceutically acceptable salt thereof

wherein:

each A is independently halo, hydroxy or carboxylate;

each B is independently halo, hydroxy, carboxylate, carbamate ester or carbonate ester,

Z is a substituted 5- or 6-membered, heterocyclic amine selected from the group consisting of pyrazole, imidazole, oxazole and pyrazine, said heterocyclic amine having at least one alkyl substituent, wherein said alkyl substituent sterically hinders access of the Pt atom to a DNA strand of a tumor cell, and wherein all substituents on the heterocycle are alkyl substituents; and

X is NH_3 or mono- or dialkyl substituted NH_3.

The complexes of this invention have greater aqueous solubility than known compounds such as cisplatin, *cis*-ammine(2-methylpyridine)dichloroplatinum(II), bis-acetato-

ammine(cyclohexylamine)dichloroplatinum(IV) and bis-butyrato-ammine(cyclohexylamine)dichloroplatinum(IV). For platinum(II) compounds of formula Ia, there is a 1.3 to 12 fold increase in aqueous solubility compared to cisplatin and *cis*-ammine(2-methylpyridine)dichloroplatinum(II) (see Table 1, examples 1-10).

For the platinum(IV) compounds of formula Ib, there is a 2.6 to 100 fold increase in solubility compared to cisplatin, bis-acetato-ammine(cyclohexylamine)dichloroplatinum(IV) and bis-butyrato-ammine(cyclohexylamine)dichloroplatinum(IV) (see Table 1, examples 11-16).

The complexes of the invention also demonstrate activity against cancer cells, particularly against cancer cells resistant to cisplatin and carboplatin. More importantly, they demonstrate less resistance than many known componds. In particular, the complexes of the invention exhibit reduced resistance factors compared to cisplatin and carboplatin. The resistance factors for cisplatin in A2780/A2780R, CH1/CH1R and 41M/41MR sets of cancer cell lines are about 16, 7 and 5, respectively. It is not, of course, surprising that the resistance factors for cisplatin itself are fairly high, but the other commercial complex, carboplatin, is also less effective with cisplatin resistant cell lines. The resistance factor for carboplatin in A2780/A2780R, CH1/CH1R and 41M/41MR sets of cancer cell lines are about 15, 5 and 3, respectively. For complexes of the invention, the resistance factors in CH1/CH1R and 41M/41MR sets of cancer cell lines are approximately 2, a 2 to 7 fold decrease compared to cisplatin. In A2780/A2780R cancer cell lines, the resistance factors for complexes of the invention ranged from 1.8 to 8, a 2 to 9 fold decrease compared to cisplatin and carboplatin. In particular, for $[PtCl_2(NH_3)(1,3,5\text{-trimethylpyrazole})]$, the resistance factor for A2780/A2780R cells was 1.8, an 8 to 9 fold decrease compared to cisplatin and carboplatin.

The complexes of the invention also exhibited comparable and, in some cancer cells, lower resistance factors than *cis*-ammine(2-methylpyridine)dichloroplatinum(II), bis-acetato-ammine(cyclohexylamine)dichloroplatinum(IV) and bis-butyrato-ammine(cyclohexylamine)dichloroplatinum(IV). For complexes of formula Ia with Z being 5-membered heterocyclic compounds with more than one heteroatom, the resistance factors were, unexpectedly, comparable to that of *cis*-ammine(2-methylpyridine)dichloroplatinum(II). In particular, complexes of formula Ia where Z is a 5-membered heterocyclic ring with more than one nitrogen heteroatom surprisingly exhibit even lower resistance factors than *cis*-ammine(2-methylpyridine)dichloroplatinum(II) in A2780/A2780R cancer cell lines. More specifically, the

complex, [$PtCl_2(NH_3)$(1,3,5-trimethylpyrazole)] exhibited a 2.6 fold decrease in resistance factor for the A2780/A2780R cell lines compared to *cis*-ammine(2-methylpyridine)dichloro-platinum(II). It was also surprising to observe that [$PtCl_2(NH_3)$(1,3,5-trimethylpyrazole)] appears to be less toxic than cisplatin and than *cis*-ammine(2-methylpyridine)dichloro-platinum(II). The maximum tolerated dose (MTD) in mice for [$PtCl_2(NH_3)$(1,3,5-trimethylpyrazole)] was greater than 50 mg/Kg. This is greater than the MTD of either cisplatin or *cis*-ammine(2-methylpyridine)dichloroplatinum(II) which doses are 11.3 mg/Kg and 40 mg/Kg, respectively. Thus, the complexes exemplified herein expand the repertoire of available spectra of characteristics available for pharmaceutical use.

Claim Amendments:

Claims 1, 14 and 15 have been amended. Claims 2, 8-13 and 21 have been cancelled. Upon entry of these amendments, claims 1, 3-7 and 14-20 will be pending in the case.

The claims were amended to facilitate prosecution. Support for the amendments can be found throughout the specification and in the originally filed claims. More particularly, support for the amendments to claim 1 can be found in the Specification on page 4, lines 23-29; page 5, lines 10-12; and page 5, lines 20-22. Support for the amendments to claim 15 can be found in the Specification at page 5, lines 16-18. Accordingly, these amendments do not introduce new matter.

Rejection Under 35 U.S.C. § 112, First paragraph:

Claims 1-16 and 18-21 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and /or use the invention. More particularly, the Examiner has indicated that the claims are not commensurate in scope as to the possibilities for the substituent "that sterically hinders access of the Pt atom to a DNA strand of a tumor cell" in the Z definition." In addition, the Examiner indicated that "the specification has no definition for "anion" for A", and concluded that, for these reasons, "the specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these broad claims".

In response to this ground for rejection and only for the purpose of facilitating prosecution, Applicants have amended claim 1. With respect to the definition of Z, Applicants have amended claim 1 to recite only four preferred heterocyclic moieties being substituted by alkyl substituents. Accordingly, the claims now cover a finite class of heterocyclic compounds with a single type of substitution. With respect to the definition of A, Applicants have amended claim 1 to recite only three preferred anion substituents.

As disclosed in the specification, testing was performed on sixteen different exemplary compounds. Although the Examiner has indicated that there was insufficient guidance for preparing additional antitumor compounds commensurate in scope with the claims, Applicants believe that the claims as amended herein warrant reconsideration of this ground for rejection. In particular, Applicants believe that adequate guidance is provided throughout the specification which would enable one of skill in the art to prepare other compounds having the four claimed heterocyclic groups and the three claimed anionic groups according to the claims, and means to select compounds for use as therapeutic agents.

Regarding the Examiner's rejection of claim 21, this rejection has been rendered moot by cancellation of claim 21 herein.

Rejection Under 35 U.S.C. § 112, Second paragraph:

Claims 1 and 15 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Regarding claim 1, the Examiner is of the opinion that claim 1 is indefinite in that the metes and bounds of "ester", "carboxylate", "carbamate" and "bi-dentate carboxylate or sulfate" in the definition of substituent B are unknown and there is no definition for these terms in the specification.

As a preliminary matter, Applicants would like to point out that the term "ester" is used in conjunction with the term "carbamate", i.e. "carbamate ester", and "carbonate", i.e. "carbonate ester", and these terms should be evaluated together, not separately. For clarity, Applicants have amended claim 1 to recite "carbamate ester or carbonate ester". Even though the specification recites "carbamate or carbonate ester" (page 5, line 6), as discussed further below, it would be clear that this phrase is synonymous with "carbamate ester or carbonate ester".

Taking these points into consideration, Applicants believe that the terms "carbamate ester", "carboxylate" and "carbonate ester" are well-known and widely used chemical terms, and that there is no need to include definitions for these terms in the specification, because their common meaning would be clear to those of skill in the art. For example, Exhibit A presents information about esters, different ways of their preparation, hydrolysis, reduction, the most common reactions of esters, etc. In particular, page 840 shows the chemical reactions that resulted in creation of carbonate ester and carbamate ester. In addition, the term "bi-dentate" appeared only in claim 2, which has been cancelled herein. Accordingly, Applicants respectfully request reconsideration of this ground for rejection.

The Examiner is also of the opinion that claim 15 is indefinite in that that it is unclear which substituent can be coupled to the heterocycle and on which position of the heterocycle. Applicants believe that claim 15 as amended herein is no longer indefinite, since it now recites the substituent (i.e. an alkyl group), and the exact position of the substitution (i.e. one atom away from the coordinating atom). Accordingly, Applicants believe that this ground for rejection has been rendered moot.

Rejection Under 35 U.S.C. § 102 over Wienkotter et al., Rochon et al, and de Oliveira et al.

Claims 1-4, 6-11, 15, 16, and 18-21 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Wienkotter (Wienkotter et al., Chem Abstract 126:311303 ("Platinum (II) nucleobase complexes containing up to four different ligands: synthesis and x-ray structure determinations of cis-[PtI(1-MeC) 2 (NH_3)]ClO_4 and [PtI(1-MeC) (9-EtGH)(NH_3)]ClO_4.cntdot.1.5H2O")); Rochon (Rochon et al., Chem Abstract 115:269138 ("Structures of the nitroimidazole platinum group metal complexes: cis-amminedibromo[1-({[(2-hydroxyethyl)amino]carbonyl}methyl)-2-nitroimidazole] platinum (II) and trans-dichlorobis(1-hydroxyethyl-2-methyl-5-nitroimidazole)palladium (II)")); and de Oliveira (de Oliveira et al., Chem Abstract 125:211928 ("New perfluorophthalate complexes of platinum (II) with chemotherapeutic potential")). More particularly, the Examiner has indicated that the instantly claimed compounds read on the compounds, disclosed in Wienkotter, Rochon and/or Oliveira The separate detailed response is given below for each of these references.

Wienkotter discloses a platinum complex where the heterocycle is a pyrimidine derivative. Claim 1 as amended recites four different heterocyclic moieties, which are: pyrazole,

imidazole, oxazole and pyrazine. Thus, as amended, claim 1 now recites a different chemical structure than Wienkotter and is no longer anticipated by the compound disclosed in Wienkotter.

Rochon discloses a platinum complex with an imidazole ring, having nitro- and acetamide substituents. Although imidazol is among the four heterocyclic moieties, recited in amended claim 1, claim 1 has also been amended herein to recite only alkyl substituents for these heterocyclic moieties. Accordingly, claim I as amended presents a different chemical composition which is no longer anticipated by the compound disclosed in Rochon.

de Oliveira discloses four platinum complexes. Two of them are based on a two-cyclic ring consisting of piperidine and benzene derivatives. The other two structures possess pyridine and oxopyridine as the heterocyclic moieties. In contrast, the claimed compounds in the instant invention are limited to pyrazole, imidazole, oxazole and pyrazine derivatives. Thus, being completely different chemical structures, the compounds recited in amended claim 1 are no longer anticipated by the compounds disclosed in de Oliveira.

Therefore, claim 1 as amended no longer reads on any of the compounds disclosed in Wienkotte, Rochon, and/or de Oliveira. Claims 2, 8-13 and 21 have been cancelled. Claims 16 and 18, being dependent on amended claim 1, and claims 19 and 20, being multiple dependent claims (depended on claims 1 and 18) are no longer anticipated by the compounds disclosed in these references. For the forementioned reasons, Applicants respectfully request reconsideration of this ground for rejection.

Rejection Under 35 U.S.C. § 102 over Skov et al. and Murrer et al.

Claims 1-16 and 18-21 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Skov and Murrer. More particularly, the Examiner has indicated that the both references teach the compounds and composition of the instant invention.

Skov (Skov et al., U.S. Patent 4,921,963) teaches square planar complexes of platinum II, containing one radiosensitizing ligand and one "amine or ammine" ligand. Those radiosensitizing ligands are selected from a mononitro-substituted pyrazole, a mononitro-substituted imidazole, a mononitro-substituted thiazole and a mononitro-substituted isothiazole (col.3, lines 37-40). As was previously stated, claim 1 as amended recites only alkyl substituents for the heterocyclic moieties listed in claim 1. Accordingly, Skov no longer anticipates the instant invention.

Murrer (Murrer et al., U.S. Patent 5,665,771) discloses only pyridine-containing compounds (col. 1, lines 39, 41). As amended herein, the claims now exclude pyridine and recite only pyrazole, imidazole, oxazole and pyrazine as the selected amines. There is no teaching or suggestion in Murrer to use these four heterocyclic moieties instead of pyridine. Additionally, all the compounds of the claimed invention are disubstituted heteroaromatic moieties (p.5, lines 10-12). Murrer only exemplifies pyridine, which is a mono-substituted heterocyclic compound. Therefore, Murrer teaches compounds which are different from those of the instant invention.

Based on the foregoing discussion, Applicants believe that the claims as amended herein are now free from the prior art cited by the Examiner and respectfully request reconsideration of this ground for rejection.

Rejection Under 35 U.S.C. § 103 over Skov

Claims 1-21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Skov. More particularly, the Examiner has indicated that Skov teaches a generic group of compounds which embraces Applicants' instantly claimed compounds and has alleged that the prior art disclosed genus of useful compounds was sufficient to render prima facie obvious a species falling within a genus.

Applicants believe that Skov teaches away from the compounds claimed in the instant invention. Skov teaches that "the nitro group is a prerequisite for activity, as it supplies the electron affinity to the ligand" (col. 5, lines 8-10). As such, there is no motivation or suggestion made by Skov to use other substituents, such as Applicants' claimed alkyl substituents instead of mononitro- substituents. Thus, Skov cannot render Applicants' claimed invention obvious. For these reasons, Applicants respectfully request reconsideration of this ground for rejection.

Rejection Under 35 U.S.C. § 103 over Murrer

Claims 1-21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Murrer. More particularly, the Examiner has indicated that Murrer teaches a generic group of compounds which embraces Applicants' instantly claimed compounds and has alleged that the genus disclosed by Murrer was sufficient to render prima facie obvious a species falling within a genus.

As amended herein, the claims now recite a select group of compounds having one of four types of heterocyclic amine moieties with alkly substituents. Murrer, in contrast, teaches

hundreds of thousands of different compounds having any type of substituted amine moiety.

In *In re Baird* (29 USPQ 2d 1550 (1994)), a generic diphenol formula was held not to render obvious a particular bisphenol compound, because "there is nothing in the disclosure of Knapp suggesting that one should select such variables. Indeed, Knapp appears to teach away from the selection of bisphenol A by focusing on more complex diphenols..." (*Id.*, at 1552.) Likewise, in the instant case, Murrer teaches a plethora of different substituted amines, and makes no suggestion to select Applicants' four claimed heterocyclic amines with alkyl substitutions. Moreover, Murrer's focus on pyridine with a single ring nitrogen teaches away from Applicants' claimed compounds each having two ring nitrogens. For these reasons, Applicants believe that Murrer does not render the claims as amended herein obvious, and respectfully request reconsideration of this ground for rejection.

III. SUMMARY

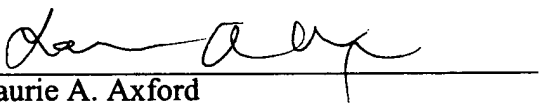
For the foregoing reasons, Applicants believe the amendments presented herein place the claims in condition for allowance. Reconsideration of the amended claims is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**".

Also attached is an Exhibit A which presents information about esters.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **39144-20043.00**.

Respectfully submitted,

Dated: April 18, 2002 By: 

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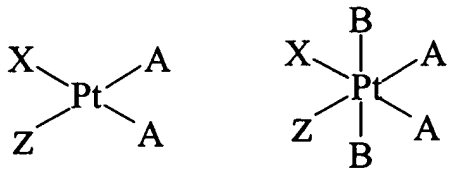
VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend the above-captioned application as follows:

In the Claims:

Please amend the claims as follows:

1. (Twice amended) A *cis*-platinum complex of the formula Ia or Ib



Ia Ib

or a pharmaceutically acceptable salt thereof

wherein:

each A is independently [an anion] halo, hydroxy or carboxylate;

each B is independently halo, hydroxy, carboxylate, carbamate ester or [a] carbonate ester;

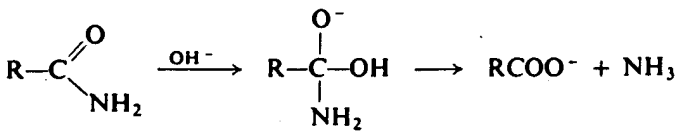
Z is a substituted 5- or 6-membered heterocyclic [moiety] amine selected from the group consisting of pyrazole, imidazole, oxazole and pyrazine, said heterocyclic amine having at least one alkyl substituent, wherein [at least one] said alkyl substituent sterically hinders access of the Pt atom to a DNA strand of a tumor cell [by a measurable amount more than an unsubstituted heterocyclic moiety with the same structure when tested under the same conditions, and wherein Z is other than pyridine], and wherein all substituents on the heterocycle are alkyl substituents; and

X is NH_3 or mono- or dialkyl substituted NH_3.

14. (Amended) The complex of claim [12] 1 wherein Z is 1,3,5-trimethylpyrazole.

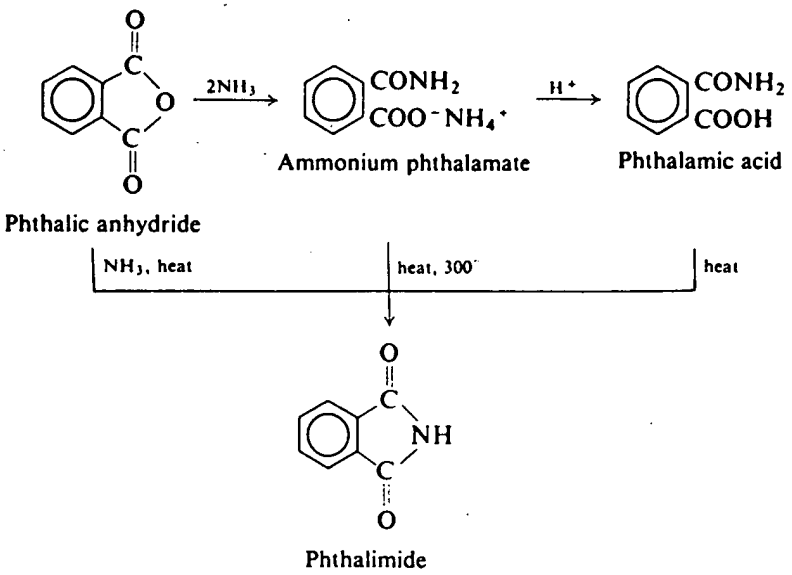
15. (Amended) The complex of claim 1 wherein said [at least one] alkyl substituent is coupled to the heterocycle at a position [other than the position adjacent to] one atom removed from the coordinating atom in said heterocycle.

Under alkaline conditions hydrolysis involves attack by the strongly nucleophilic hydroxide ion on the amide itself:



20.14 Imides

Like other anhydrides, cyclic anhydrides react with ammonia to yield amides; in this case the product contains both $-CONH_2$ and $-COOH$ groups. If this acid–amide is heated, a molecule of water is lost, a ring forms, and a product is obtained in which two acyl groups have become attached to nitrogen; compounds of this sort are called **imides**. Phthalic anhydride gives *phthalamic acid* and *phthalimide*:



Problem 20.10 Outline all steps in the synthesis of *succinimide* from succinic acid.

Problem 20.11 Account for the following sequence of acidities. (*Hint*: See Sec. 19.12.)

	K_a
Ammonia	10^{-33}
Benzamide	10^{-14} to 10^{-15}
Phthalimide	5×10^{-9}

ESTERS

20.15 Preparation of esters

Esters are usually prepared by the reaction of alcohols or phenols with acids or acid derivatives. The most common methods are outlined below.

PREPARATION OF ESTERS

1. From acids. Discussed in Secs. 19.16 and 20.18.

$$\underset{\substack{\text{Carboxylic acid}\\ \text{R } \textit{may be alkyl or aryl}}}{\text{RCOOH}} + \underset{\substack{\text{Alcohol}\\ \text{R' } \textit{is usually alkyl}}}{\text{R'OH}} \underset{}{\overset{\text{H}^+}{\rightleftharpoons}} \underset{\text{Ester}}{\text{RCOOR'}} + \text{H}_2\text{O}$$

Reactivity of R'OH: $1° > 2° (> 3°)$

Examples:

$$\underset{\text{Acetic acid}}{\text{CH}_3\text{COOH}} + \underset{\text{Benzyl alcohol}}{\text{HOCH}_2\text{C}_6\text{H}_5} \overset{\text{H}^+}{\rightleftharpoons} \underset{\text{Benzyl acetate}}{\text{CH}_3\text{COOCH}_2\text{C}_6\text{H}_5}$$

$$\underset{\text{Benzoic acid}}{\text{C}_6\text{H}_5\text{COOH}} + \underset{\substack{\text{Isobutyl}\\ \text{alcohol}}}{\text{HOCH}_2\text{CH(CH}_3)_2} \overset{\text{H}^+}{\rightleftharpoons} \underset{\text{Isobutyl benzoate}}{\text{C}_6\text{H}_5\text{COOCH}_2\text{CH(CH}_3)_2}$$

2. From acid chlorides or anhydrides. Discussed in Secs. 20.8 and 20.10.

$$\text{RCOCl} + \text{R'OH (or ArOH)} \longrightarrow \text{RCOOR' (or RCOOAr)} + \text{HCl}$$

$$(\text{RCO})_2\text{O} + \text{R'OH (or ArOH)} \longrightarrow \text{RCOOR' (or RCOOAr)} + \text{RCOOH}$$

Examples:

$$\underset{\substack{o\text{-Bromobenzoyl}\\ \text{chloride}}}{o\text{-BrC}_6\text{H}_4\text{COCl}} + \text{C}_2\text{H}_5\text{OH} \xrightarrow{\text{pyridine}} \underset{\text{Ethyl } o\text{-bromobenzoate}}{o\text{-BrC}_6\text{H}_4\text{COOC}_2\text{H}_5} + \text{HCl}$$

$$\underset{\substack{\text{Acetic}\\ \text{anhydride}}}{(\text{CH}_3\text{CO})_2\text{O}} + \underset{p\text{-Nitrophenol}}{p\text{-HOC}_6\text{H}_4\text{NO}_2} \xrightarrow{\text{NaOH}} \underset{p\text{-Nitrophenyl acetate}}{p\text{-CH}_3\text{COOC}_6\text{H}_4\text{NO}_2} + \text{CH}_3\text{COOH}$$

3. From esters. Transesterification. Discussed in Sec. 20.20. ▣

The direct reaction of alcohols or phenols with acids involves an equilibrium and—especially in the case of phenols—requires effort to drive to completion (see Sec. 19.16). In the laboratory, reaction with an acid chloride or anhydride is more commonly used.

The effect of the structure of the alcohol and of the acid on ease of esterification has already been discussed (Sec. 19.16).

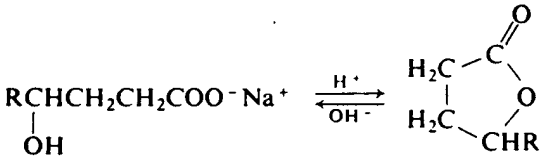
Table 20.2 ESTERS OF CARBOXYLIC ACIDS

Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Methyl acetate	−98	57.5	Ethyl formate	−80	54
Ethyl acetate	−84	77	Ethyl acetate	−84	77
n-Propyl acetate	−92	102	Ethyl propionate	−74	99
n-Butyl acetate	−77	126	Ethyl *n*-butyrate	−93	121
n-Pentyl acetate		148	Ethyl *n*-valerate	−91	146
Isopentyl acetate	−78	142	Ethyl stearate	34	215[15]
Benzyl acetate	−51	214	Ethyl phenylacetate		226
Phenyl acetate		196	Ethyl benzoate	−35	213

As was mentioned earlier, esterification using aromatic acid chlorides, ArCOCl, is often carried out in the presence of base (the Schotten-Baumann technique, Sec. 20.8).

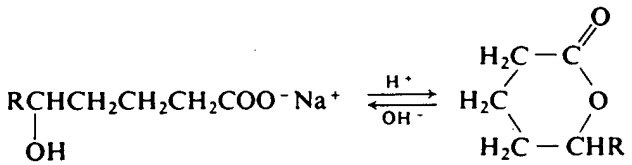
Problem 20.12 When benzoic acid is esterified by methanol in the presence of a little sulfuric acid, the final reaction mixture contains five substances: benzoic acid, methanol, water, methyl benzoate, sulfuric acid. Outline a procedure for the separation of the pure ester.

A hydroxy acid is both alcohol and acid. In those cases where a five- or six-membered ring can be formed, *intramolecular* esterification occurs. Thus, a γ- or δ-hydroxy acid loses water spontaneously to yield a cyclic ester known as a **lactone**. Treatment with base (actually hydrolysis of an ester) rapidly opens the lactone ring



Salt of a γ-hydroxy acid — A γ-lactone

A cyclic ester: five-membered ring



Salt of a δ-hydroxy acid — A δ-lactone

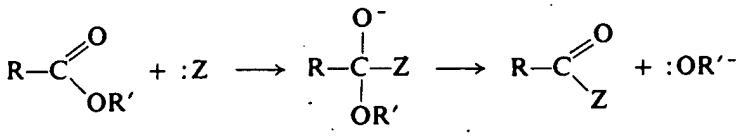
A cyclic ester: six-membered ring

to give the open-chain salt. We shall encounter lactones again in our study of carbohydrates (Sec. 28.8).

Problem 20.13 Suggest a likely structure for the product formed by heating each of these acids. (a) *Lactic acid*, $CH_3CHOHCOOH$, gives *lactide*, $C_6H_8O_4$. (b) 10-Hydroxydecanoic acid gives a material of high molecular weight (1000–9000).

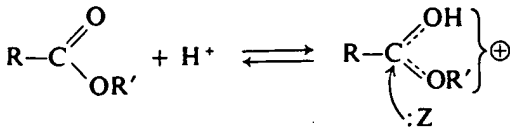
20.16 Reactions of esters

Esters undergo the nucleophilic substitution that is typical of carboxylic acid derivatives. Attack occurs at the electron-deficient carbonyl carbon, and results in the replacement of the —OR′ group by —OH, —OR″, or —NH_2:



:Z = $:OH^-$, $:OR''^-$, $:NH_3$

These reactions are sometimes carried out in the presence of acid. In these acid-catalyzed reactions, H^+ attaches itself to the oxygen of the carbonyl group, and thus renders carbonyl carbon even more susceptible to nucleophilic attack.

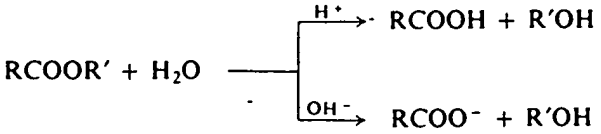


Acid catalysis: *makes carbon more susceptible to nucleophilic attack*

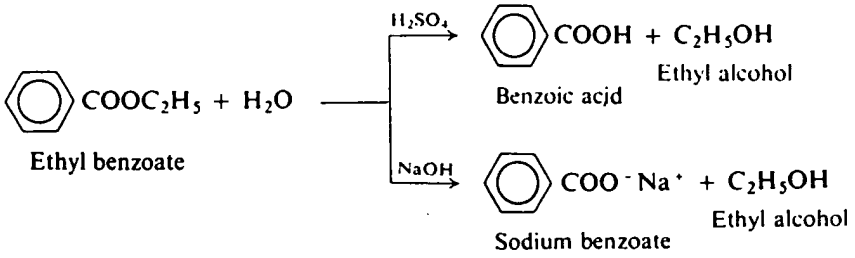
REACTIONS OF ESTERS

1. Conversion into acids and acid derivatives.

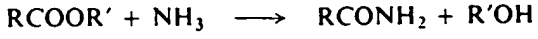
(a) Conversion into acids. Hydrolysis. Discussed in Secs. 20.17 and 20.18.



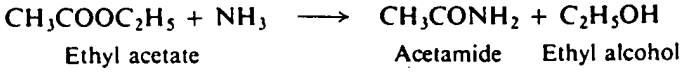
Example:



(b) Conversion into amides. Ammonolysis. Discussed in Sec. 20.19.



Example:



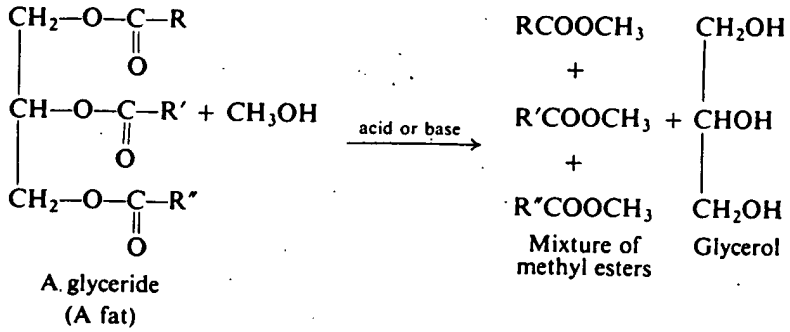
CONT.

CONT.

(c) C nversion into esters. Transesterification. Alcoholysis. Discussed in Sec. 20.20.

$$RCOOR' + R''OH \underset{}{\overset{\text{acid or base}}{\rightleftharpoons}} RCOOR'' + R'OH$$

Example:



A glyceride
(A fat)

2. **Reaction with Grignard reagents.** Discussed in Sec. 20.21.

$$RCOOR' + 2R''MgX \longrightarrow R-\underset{\displaystyle OH}{\overset{\displaystyle R''}{\underset{|}{\overset{|}{C}}}}-R''$$

Tertiary alcohol

Example:

$$CH_3CH(CH_3)COOC_2H_5 + 2CH_3MgI \longrightarrow CH_3CH(CH_3)-\underset{\displaystyle OH}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-CH_3$$

Ethyl isobutyrate; Methylmagnesium iodide, *2 moles*; 2,3-Dimethyl-2-butanol

3. **Reduction to alcohols.** Discussed in Sec. 20.22.

(a) **Catalytic hydrogenation. Hydrogenolysis**

$$RCOOR' + 2H_2 \xrightarrow[\substack{250^\circ \\ 3000\text{–}6000\ \text{lb/in.}^2}]{CuO.\ CuCr_2O_4} RCH_2OH + R'OH$$

1° alcohol

Example:

$$CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-COOC_2H_5 + 2H_2 \xrightarrow[250^\circ,\ 3300\ \text{lb/in.}^2]{CuO.\ CuCr_2O_4} CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-CH_2OH + C_2H_5OH$$

Ethyl trimethylacetate
(Ethyl 2,2-dimethylpropanoate)

Neopentyl alcohol
(2,2-Dimethylpropanol)

Ethyl alcohol

CONT.

CONT.

(b) Chemical reduction

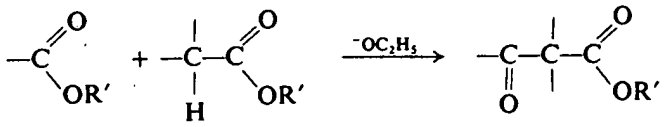
$$4RCOOR' + 2LiAlH_4 \xrightarrow{\text{anyhd. ether}} \left\{\begin{matrix} LiAl(OCH_2R)_4 \\ + \\ LiAl(OR')_4 \end{matrix}\right\} \xrightarrow{H^+} \left\{\begin{matrix} RCH_2OH \\ + \\ R'OH \end{matrix}\right\}$$

Example:

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOCH_3 \xrightarrow{LiAlH_4} CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2OH$$

Methyl oleate (Methyl *cis*-9-octadecenoate) — Oleyl alcohol (*cis*-9-Octadecen-1-ol)

4. Reaction with carbanions. Claisen condensation. Discussed in Secs. 21.11 and 21.12.

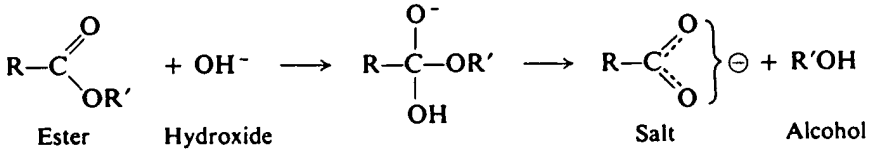


A β-keto ester ▣

20.17 Alkaline hydrolysis of esters

A carboxylic ester is hydrolyzed to a carboxylic acid and an alcohol or phenol when heated with aqueous acid or aqueous base. Under alkaline conditions, of course, the carboxylic acid is obtained as its salt, from which it can be liberated by addition of mineral acid.

Base promotes hydrolysis of esters by providing the strongly nucleophilic reagent OH^-. This reaction is essentially irreversible, since a resonance-stabilized



Ester — Hydroxide — Salt — Alcohol

carboxylate anion (Sec. 19.13) shows little tendency to react with an alcohol.

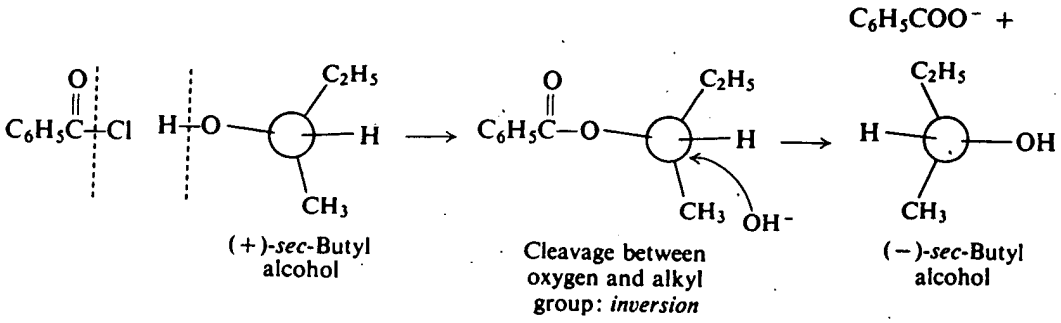
Let us look at the various aspects of the mechanism we have written, and see what evidence there is for each of them.

First, reaction involves attack on the ester by hydroxide ion. This is consistent with the **kinetics**, which is second-order, with the rate depending on both ester concentration and hydroxide concentration.

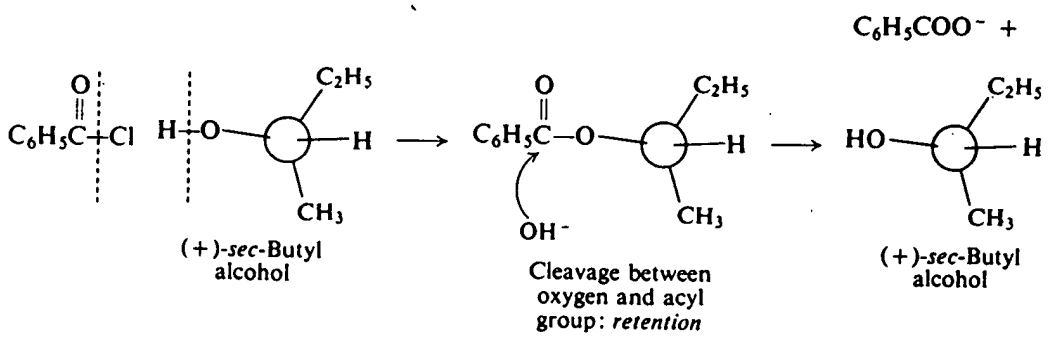
Next hydroxide attacks at the carbonyl carbon and displaces alkoxide ion. That is to say, reaction involves cleavage of the bond between oxygen and the acyl group, RCO–OR'. For this there are two lines of evidence, the first being the **stereochemistry**.

Let us consider, for example, the formation and subsequent hydrolysis of an ester of optically active *sec*-butyl alcohol. Reaction of (+)-*sec*-butyl alcohol with

benzoyl chloride must involve cleavage of the hydrogen–oxygen bond and hence cannot change the configuration about the chiral center (see Sec. 4.23). If hydrolysis of this ester involves cleavage of the bond between oxygen and the *sec*-butyl group, we would expect almost certainly inversion (or inversion plus racemization if the reaction goes by an S_N1 type of mechanism):

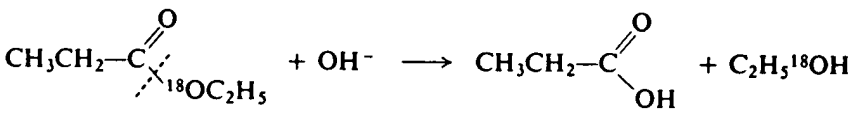


If, on the other hand, the bond between oxygen and the *sec*-butyl group remains intact during hydrolysis, then we would expect to obtain *sec*-butyl alcohol of the same configuration as the starting material:



When *sec*-butyl alcohol of rotation +13.8° was actually converted into the benzoate and the benzoate was hydrolyzed in alkali, there was obtained *sec*-butyl alcohol of rotation +13.8°. This complete retention of configuration strongly indicates that bond cleavage occurs between oxygen and the acyl group.

Tracer studies have confirmed the kind of bond cleavage indicated by the stereochemical evidence. When ethyl propionate labeled with ^{18}O was hydrolyzed by base in ordinary water, the ethanol produced was found to be enriched in ^{18}O; the propionic acid contained only the ordinary amount of ^{18}O:

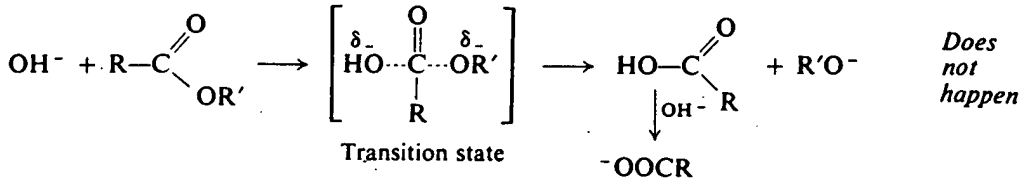


The alcohol group retained the oxygen that it held in the ester; cleavage occurred between oxygen and the acyl group.

The study of a number of other hydrolyses by both tracer and stereochemical methods has shown that cleavage between oxygen and the acyl group is the usual one in ester hydrolysis. This behavior indicates that the preferred point of nucleophilic attack is the carbonyl carbon rather than the alkyl carbon; this is, of

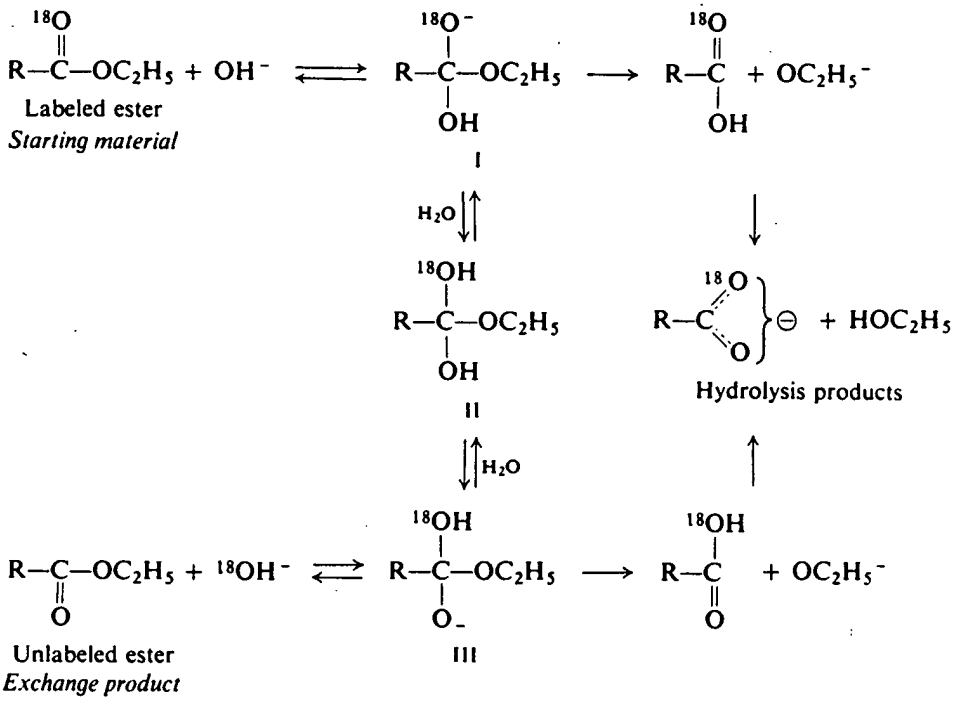
course, what we might have expected in view of the generally greater reactivity of carbonyl carbon (Sec. 20.5).

Finally, according to the mechanism, attack by hydroxide ion on carbonyl carbon does not displace alkoxide ion in one step,



but rather in *two steps* with the intermediate formation of a tetrahedral compound. These alternative mechanisms were considered more or less equally likely until 1950 when elegant work on **isotopic exchange** was reported by Myron Bender (now at Northwestern University).

Bender carried out the alkaline hydrolysis of carbonyl-labeled ethyl benzoate, $C_6H_5C^{18}OOC_2H_5$, in ordinary water, and focused his attention, not on the product, but on the *reactant*. He interrupted the reaction after various periods of time, and isolated the unconsumed ester and analyzed it for ^{18}O content. He found that in the alkaline solution the ester was undergoing not only hydrolysis but also *exchange of its ^{18}O for ordinary oxygen from the solvent.*



Oxygen exchange is not consistent with the one-step mechanism, which provides no way for it to happen. Oxygen exchange is consistent with a two-step mechanism in which intermediate I is not only formed, but partly reverts into starting material and partly is converted (probably via the neutral species II) into III—an intermediate that is equivalent to I except for the position of the label. If all this is so, the "reversion" of intermediate III into "starting material" yields ester that has lost its ^{18}O.

Bender's work does not *prove* the mechanism we have outlined. Conceivably, oxygen exchange—and hence the tetrahedral intermediate—simply represent a blind-alley down which ester molecules venture but which does not lead to hydrolysis. Such coincidence is unlikely, however, particularly in light of certain kinetic relationships between oxygen exchange and hydrolysis.

Similar experiments have indicated the reversible formation of tetrahedral intermediates in hydrolysis of other esters, amides, anhydrides, and acid chlorides, and are the basis of the general mechanism we have shown for nucleophilic acyl substitution.

Exchange experiments are also the basis of our estimate of the relative importance of the two steps: differences in rate of hydrolysis of acyl derivatives depend chiefly on how fast intermediates are formed, and also on what fraction of the intermediate goes on to product. As we have said, the rate of formation of the intermediate is affected by both electronic and steric factors: in the transition state, a negative charge is developing and carbon is changing from trigonal toward tetrahedral.

Even in those cases where oxygen exchange cannot be detected, we cannot rule out the possibility of an intermediate; it may simply be that it goes on to hydrolysis products much faster than it does anything else.

Problem 20.14 The relative rates of alkaline hydrolysis of ethyl *p*-substituted benzoates, *p*-$GC_6H_4COOC_2H_5$, are:

$$\underset{}{G = NO_2} > \underset{}{Cl} > \underset{}{H} > \underset{}{CH_3} > \underset{}{OCH_3}$$
$$\underset{110}{} \quad \underset{4}{} \quad \underset{1}{} \quad \underset{0.5}{} \quad \underset{0.2}{}$$

(a) How do you account for this order of reactivity? (b) What kind of effect, activating or deactivating, would you expect from *p*-Br? from *p*-NH_2? from *p*-$C(CH_3)_3$? (c) Predict the order of reactivity toward alkaline hydrolysis of: *p*-aminophenyl acetate, *p*-methylphenyl acetate, *p*-nitrophenyl acetate, phenyl acetate.

Problem 20.15 The relative rates of alkaline hydrolysis of alkyl acetates, CH_3COOR, are:

$$\underset{}{R = CH_3} > \underset{}{C_2H_5} > \underset{}{(CH_3)_2CH} > \underset{}{(CH_3)_3C}$$
$$\underset{1}{} \quad \underset{0.6}{} \quad \underset{0.15}{} \quad \underset{0.008}{}$$

(a) What two factors might be at work here? (b) Predict the order of reactivity toward alkaline hydrolysis of: methyl acetate, methyl formate, methyl isobutyrate, methyl propionate, and methyl trimethylacetate.

Problem 20.16 Exchange experiments show that the fraction of the tetrahedral intermediate that goes on to products follows the sequence:

acid chloride > acid anhydride > ester > amide

What is one factor that is probably at work here?

20.18 Acidic hydrolysis of esters

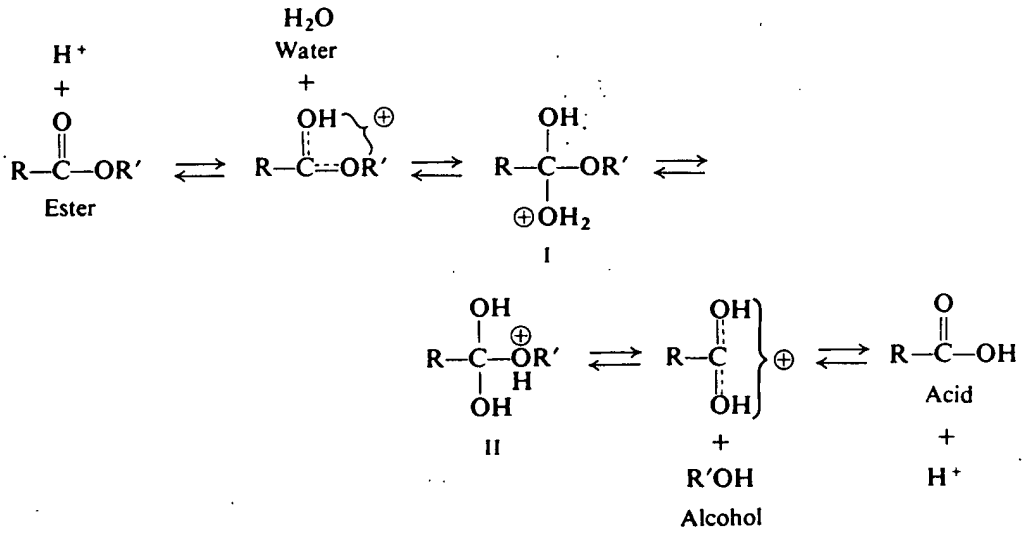
Hydrolysis of esters is promoted not only by base but also by acid. Acidic hydrolysis, as we have seen (Sec. 19.16), is reversible,

$$RCOOR' + H_2O \underset{H^+}{\overset{H^+}{\rightleftharpoons}} RCOOH + R'OH$$

and hence the mechanism for hydrolysis is also—taken in the opposite direction—

the mechanism for esterification. Any evidence about one reaction must apply to both.

The mechanism for acid-catalyzed hydrolysis and esterification is contained in the following equilibria:



Mineral acid speeds up both processes by protonating carbonyl oxygen and thus rendering carbonyl carbon more susceptible to nucleophilic attack (Sec. 20.4). In hydrolysis, the nucleophile is a water molecule and the leaving group is an alcohol; in esterification, the roles are exactly reversed.

As in alkaline hydrolysis, there is almost certainly a tetrahedral intermediate—or, rather, several of them. The existence of more than one intermediate is required by, among other things, the reversible nature of the reaction. Looking only at hydrolysis, intermediate II is *likely*, since it permits separation of the weakly basic alcohol molecule instead of the strongly basic alkoxide ion; but consideration of esterification shows that II almost certainly *must* be involved, since it is the product of attack by alcohol on the protonated acid.

The evidence for the mechanism is much the same as in alkaline hydrolysis. The position of cleavage, RCO┆OR′ and RCO┆OH, has been shown by ^{18}O studies of both hydrolysis and esterification. The existence of the tetrahedral intermediates was demonstrated, as in the alkaline reaction, by ^{18}O exchange between the carbonyl oxygen of the ester and the solvent.

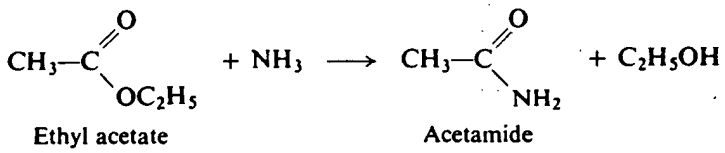
Problem 20.17 Write the steps to account for exchange between $RC^{18}OOR'$ and H_2O in acidic solution. There is reason to believe that a key intermediate here is identical with one in alkaline hydrolysis. What might this intermediate be?

Problem 20.18 Account for the fact (Sec. 19.16) that the presence of bulky substituents in either the alcohol group or the acid group slows down both esterification and hydrolysis.

Problem 20.19 Acidic hydrolysis of *tert*-butyl acetate in water enriched in ^{18}O has been found to yield *tert*-butyl alcohol enriched in ^{18}O and acetic acid containing ordinary oxygen. Acidic hydrolysis of the acetate of optically active 3,7-dimethyl-3-octanol has been found to yield alcohol of much lower optical purity than the starting alcohol, and having the opposite sign of rotation. (a) How do you interpret these two sets of results? (b) Is it surprising that these particular esters should show this kind of behavi r?

20.19 Ammonolysis of esters

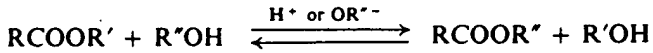
Treatment of an ester with ammonia, generally in ethyl alcohol solution, yields the amide. This reaction involves nucleophilic attack by a base, ammonia, on the electron-deficient carbon; the alkoxy group, —OR′, is replaced by —NH_2. For example:



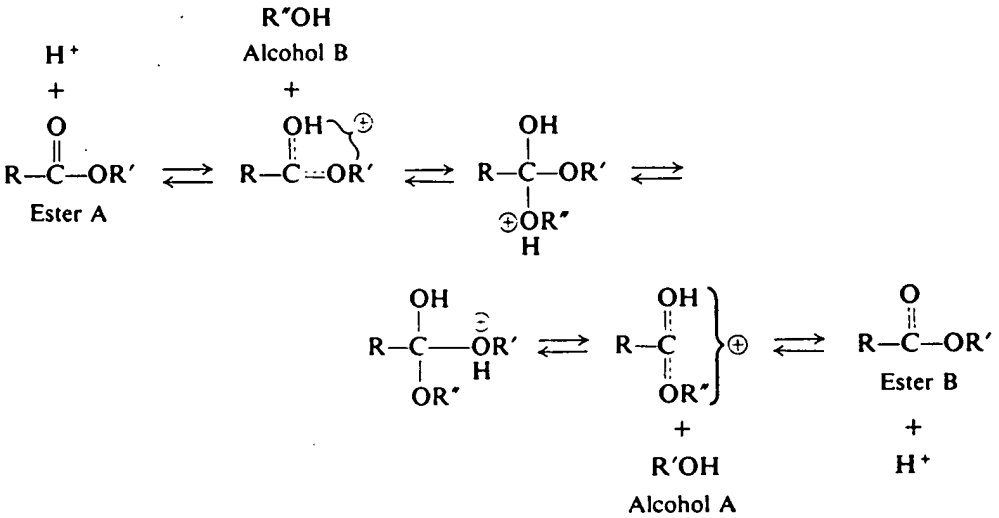
Ethyl acetate Acetamide

20.20 Transesterification

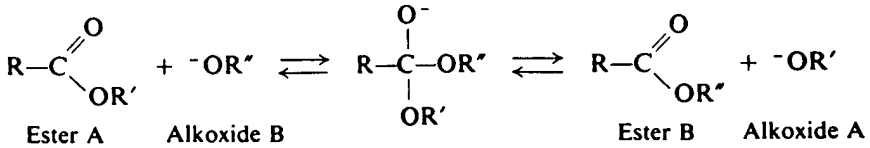
In the esterification of an acid, an alcohol acts as a nucleophilic reagent; in hydrolysis of an ester, an alcohol is displaced by a nucleophilic reagent. Knowing this, we are not surprised to find that one alcohol is capable of displacing another alcohol from an ester. This *alcoholysis* (cleavage by an alcohol) of an ester is called **transesterification**.



Transesterification is catalyzed by acid (H_2SO_4 or dry HCl) or base (usually alkoxide ion). The mechanisms of these two reactions are exactly analogous to those we have already studied. For acid-catalyzed transesterification:



For base-catalyzed transesterfication:



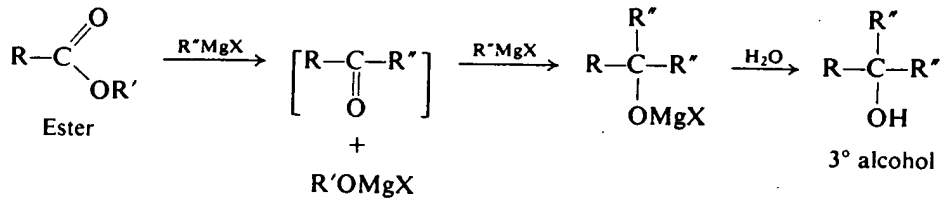
Ester A Alkoxide B Ester B Alkoxide A

Transesterification is an equilibrium reaction. To shift the equilibrium to the right, it is necessary to use a large excess of the alcohol whose ester we wish to

make, or else to remove one of the products from the reaction mixture. The second approach is the better one when feasible, since in this way the reaction can be driven to completion.

20.21 Reaction of esters with Grignard reagents

The reaction of carboxylic esters with Grignard reagents is an excellent method for preparing tertiary alcohols. As in the reaction with aldehydes and ketones (Sec. 18.11), the nucleophilic (basic) alkyl or aryl group of the Grignard reagent attaches itself to the electron-deficient carbonyl carbon. Expulsion of the alkoxide group would yield a ketone, and in certain special cases ketones are indeed isolated from this reaction. However, as we know, ketones themselves readily react with Grignard reagents to yield tertiary alcohols (Sec. 10.13); in the present case the products obtained correspond to the addition of the Grignard reagent to such a ketone:



Two of the three groups attached to the carbon bearing the hydroxyl group in the alcohol come from the Grignard reagent and hence must be identical; this, of course, places limits upon the alcohols that can be prepared by this method. But, where applicable, reaction of a Grignard reagent with an ester is preferred to reaction with a ketone because esters are generally more accessible.

Problem 20.20 Starting from valeric acid, and using any needed reagents, outline the synthesis of 3-ethyl-3-heptanol via the reaction of a Grignard reagent with: (a) a ketone; (b) an ester.

Problem 20.21 (a) Esters of which acid would yield *secondary* alcohols on reaction with Grignard reagents? (b) Starting from alcohols of four carbons or fewer, outline all steps in the synthesis of 4-heptanol.

20.22 Reduction of esters

Like many organic compounds, esters can be reduced in two ways: (a) by catalytic hydrogenation using molecular hydrogen, or (b) by chemical reduction. In either case, the ester is cleaved to yield (in addition to the alcohol or phenol from which it was derived) a primary alcohol corresponding to the acid portion of the ester.

$$\underset{\text{Ester}}{RCOOR'} \xrightarrow{\text{reduction}} \underset{\text{1° alcohol}}{RCH_2OH} + R'OH$$

Hydrogenolysis (cleavage by hydrogen) of an ester requires more severe conditions than simple hydrogenation of (addition of hydrogen to) a carbon–carbon double bond. High pressures and elevated temperatures are required: the catalyst

used most often is a mixture of oxides known as *copper chromite*, of approximately the composition $CuO.CuCr_2O_4$. For example:

$$\underset{\text{Methyl laurate}}{\underset{\text{(Methyl dodecanoate)}}{CH_3(CH_2)_{10}COOCH_3}} \xrightarrow[150°,\ 5000\ lb/in.^2]{H_2,\ CuO.CuCr_2O_4} \underset{\text{Lauryl alcohol}}{\underset{\text{(1-Dodecanol)}}{CH_3(CH_2)_{10}CH_2OH}} + CH_3OH$$

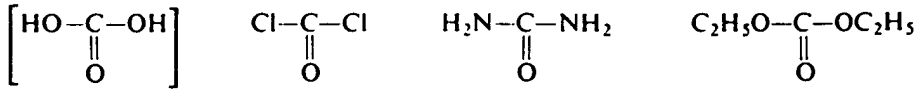
Chemical reduction is carried out by use of sodium metal and alcohol, or more usually by use of lithium aluminum hydride. For example:

$$\underset{\text{Ethyl palmitate}}{\underset{\text{(Ethyl hexadecanoate)}}{CH_3(CH_2)_{14}COOC_2H_5}} \xrightarrow{LiAlH_4} \underset{\text{1-Hexadecanol}}{CH_3(CH_2)_{14}CH_2OH}$$

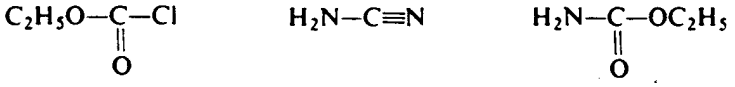
Problem 20.22 Predict the products of the hydrogenolysis of *n*-butyl oleate over copper chromite.

20.23 Functional derivatives of carbonic acid

Much of the chemistry of the functional derivatives of carbonic acid is already quite familiar to us through our study of carboxylic acids. The first step in dealing with one of these compounds is to recognize just how it is related to the parent acid. Since carbonic acid is bifunctional, each of its derivatives, too, contains two functional groups; these groups can be the same or different. For example:

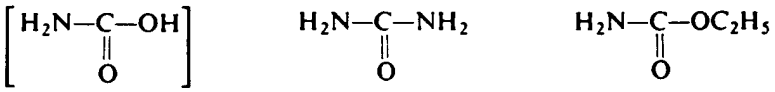


Carbonic acid (*Acid*) — Phosgene (Carbonyl chloride) (*Acid chloride*) — Urea (Carbamide) (*Amide*) — Ethyl carbonate (*Ester*)



Ethyl chlorocarbonate (*Acid chloride-ester*) — Cyanamide (*Amide-nitrile*) — Urethane (Ethyl carbamate) (*Ester-amide*)

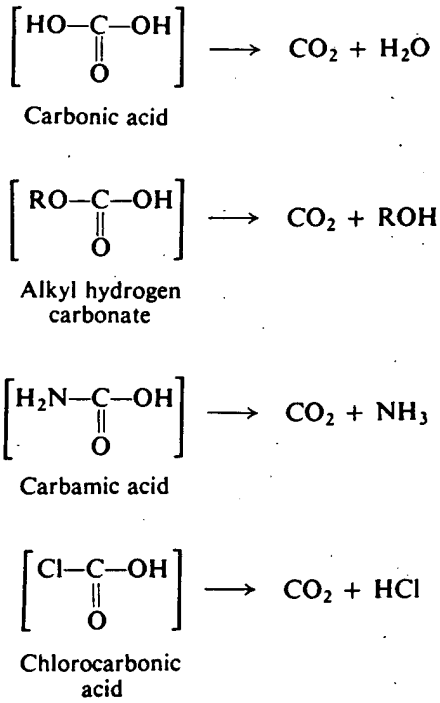
We use these functional relationships to carbonic acid simply for convenience. Many of these compounds could just as well be considered as derivatives of other acids, and, indeed, are often so named. For example:



Carbamic acid (*Acid*) — Carbamide (*Amide*) — Ethyl carbamate (*Ester*)

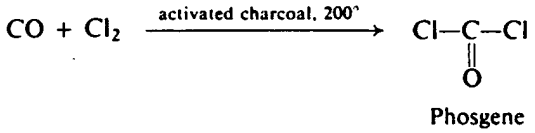
[HO—C≡N] Cyanic acid (*Acid*) — $H_2N-C\equiv N$ Cyanamide (*Amide*)

In general, a derivative of carbonic acid containing an —OH group is unstable, and decomposes to carbon dioxide. For example:

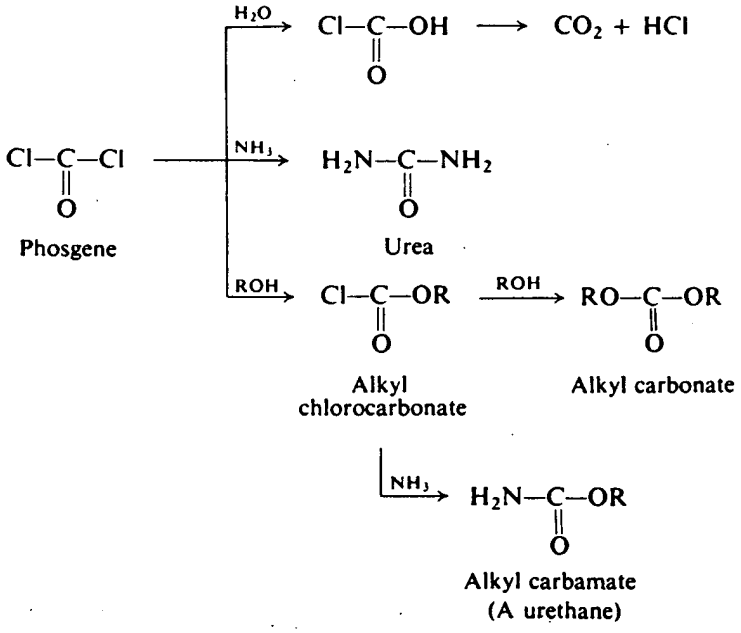


Most derivatives of carbonic acid are made from one of three industrially available compounds: phosgene, urea, or cyanamide.

Phosgene, $COCl_2$, a highly poisonous gas, is manufactured by the reaction between carbon monoxide and chlorine.



It undergoes the usual reactions of an acid chloride.



Problem 20.23 Suggest a possible synthesis of (a) 2-pentylurethane, $H_2NCOOCH(CH_3)(n\text{-}C_3H_7)$, used as a hypnotic; (b) benzyl chlorocarbonate (*carbobenzoxy chloride*), $C_6H_5CH_2OCOCl$, used in the synthesis of peptides (Sec. 30.10).

Urea, H_2NCONH_2, is excreted in the urine as the chief nitrogen-containing end product of protein metabolism. It is synthesized on a large scale for use as a fertilizer and as a raw material in the manufacture of urea–formaldehyde plastics and of drugs.

$$CO_2 + 2NH_3 \rightleftharpoons \underset{\text{Ammonium carbamate}}{H_2NCOONH_4} \xrightleftharpoons{\text{heat, pressure}} \underset{\text{Urea}}{H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2}$$

Urea is weakly basic, forming salts with strong acids. The fact that it is a stronger base than ordinary amides is attributed to resonance stabilization of the cation:

$$H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2 + H^+ \rightleftharpoons \left[H_2N{-}\overset{\overset{\oplus OH}{\|}}{C}{-}NH_2 \quad H_2\overset{\oplus}{N}{=}\overset{\overset{OH}{|}}{C}{-}NH_2 \quad H_2N{-}\overset{\overset{OH}{|}}{C}{=}\overset{\oplus}{N}H_2 \right]$$

$$\textit{equivalent to} \quad \left\{ H_2N{=}\overset{\overset{OH}{:}}{C}{=}NH_2 \right\}^{\oplus}$$

Problem 20.24 Account for the fact that *guanidine*, $(H_2N)_2C{=}NH$, is strongly basic.

Urea undergoes hydrolysis in the presence of acids, bases, or the enzyme *urease* (isolable from jack beans; generated by many bacteria, such as *Micrococcus ureae*).

$$\underset{\text{Urea}}{H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2} \xrightarrow{H_2O} \begin{cases} \xrightarrow{H^+} NH_4^+ + CO_2 \\ \xrightarrow{OH^-} NH_3 + CO_3^{--} \\ \xrightarrow{\text{urease}} NH_3 + CO_2 \end{cases}$$

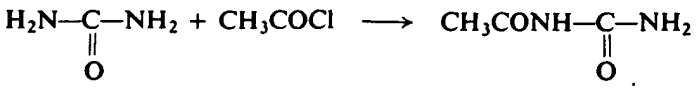
Urea reacts with nitrous acid to yield carbon dioxide and nitrogen; this is a useful way to destroy excess nitrous acid in diazotizations (Sec. 23.13).

$$H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2 \xrightarrow{HONO} CO_2 + N_2$$

Urea is converted by hypohalites into nitrogen and carbonate.

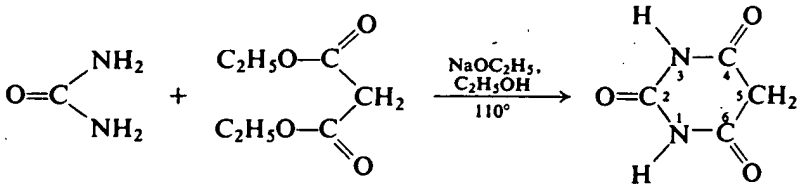
$$H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2 \xrightarrow{Br_2,\,OH^-} N_2 + CO_3^{--} + Br^-$$

Treatment of urea with acid chlorides or anhydrides yields **ureides**. Of special



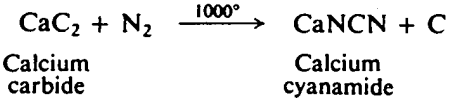
Acetylurea
A ureide

importance are the cyclic ureides formed by reaction with malonic esters; these are known as **barbiturates** and are important hypnotics (sleep-producers). For example:



Urea Ethyl malonate Barbituric acid (Malonylurea)

Cyanamide, $H_2N—C{\equiv}N$, is obtained in the form of its calcium salt by the high-temperature reaction between calcium carbide and nitrogen. This reaction is



Calcium carbide Calcium cyanamide

important as a method of nitrogen fixation; calcium cyanamide has been used as a fertilizer, releasing ammonia by the action of water.

Problem 20.25 Give the electronic structure of the cyanamide anion, $(NCN)^{--}$. Discuss its molecular shape, bond lengths, and location of charge.

Problem 20.26 Give equations for the individual steps probably involved in the conversion of calcium cyanamide into ammonia in the presence of water. What other product or products will be formed in this process? Label each step with the name of the fundamental reaction type to which it belongs.

Problem 20.27 Cyanamide reacts with water in the presence of acid or base to yield urea; with methanol in the presence of acid to yield methylisourea, $H_2NC(=NH)OCH_3$; with hydrogen sulfide to yield *thiourea*, $H_2NC(=S)NH_2$; and with ammonia to yield *guanidine*, $H_2NC(=NH)NH_2$. (a) What functional group of cyanamide is involved in each of these reactions? (b) To what general class of reaction do these belong? (c) Show the most probable mechanisms for these reactions, pointing out the function of acid or base wherever involved.

20.24 Step-reaction polymerization. Polyesters. Urea–formaldehyde resins. Polyurethanes

Carboxylic acids react with alcohols to form esters. When an acid that contains more than one —COOH group reacts with an alcohol that contains more than one —OH group, then the products are *polyesters*. For example: